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⑪ Publication number:

0 128 736  
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## EUROPEAN PATENT APPLICATION

㉑ Application number: 84303793.8

㉓ Int. Cl.<sup>3</sup>: C 07 D 277/18, C 07 D 277/48  
// A61K31/425

㉒ Data of filing: 05.06.84

㉔ Priority: 07.06.83 JP 102206/83

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㉖ Date of publication of application: 19.12.84  
Bulletin 84/51

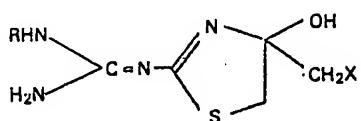
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㉚ Novel 2-guanidinothiazoline compounds, their preparation, and their use as intermediates.

㉛ Novel 2-guanidinothiazoline compounds of the general  
formula



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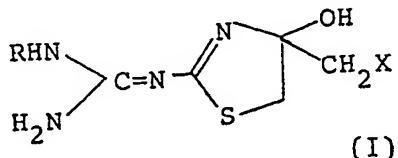
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wherein R represents a hydrogen atom or a lower alkyl group,  
and X represents a halogen atom, and the acid addition salts  
thereof; they are important intermediate compounds for pre-  
paring famotidine and thiotide which are medicaments useful  
as gastric acid secretion inhibitors.

NOVEL 2-GUANIDINOThIAZOLINE COMPOUNDS,  
THEIR PREPARATION, AND THEIR USE AS  
INTERMEDIATES

The present invention relates to novel  
2-guanidinothiazoline compounds and acid addition  
salts thereof.

According to this invention, there are  
provided 2-guanidinothiazoline compounds of the  
5 general formula



10 Wherein R represents a hydrogen atom or a lower alkyl group, and X represents a halogen atom.

15 The term "lower" in the above definition means a straight or branched carbon chain having 1-5 carbon atoms. Suitable lower alkyl groups include a methyl group, an ethyl group, an isopropyl group, a butyl group, etc. The halogen atoms may e.g. be chlorine, bromine or iodine.

20 Furthermore, the compounds of the general formula I

can form acid addition salts and there also exist the tautomers thereof. The invention includes such acid addition salts and tautomers.

5           The acid addition salts include the salts of the compounds with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, etc., and with aliphatic carboxylic acids, for example, acetic acid, maleic acid, fumaric acid, etc.

10          The compounds of the general formula I and the acid addition salts thereof provided by this invention are important intermediate compounds useful for preparing famotidine (cf. unexamined Japanese patent applications laid open under Nos. 56-22770 and

15          56-55383) and thiotidine (cf. unexamined Japanese patent application laid open under No. 53-147069) which are useful compounds for medical purposes as histamine H-2 receptor blockers or gastric acid secretion inhibitors.

20          Hitherto, as an intermediate compound for preparing such compounds, 2-guanidino-4-chloromethylthiazole (hereinafter referred to as "Compound A") is known from unexamined Japanese patent application laid-open under No.

25          53-147069. However, Compound A is undesirable in that handling of the same is complicated since it has an irritative odor and

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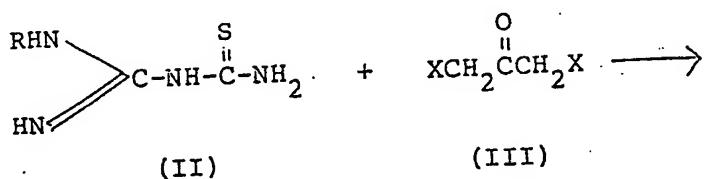
causes contact dermatitis.

When the compounds of this invention shown by general formula I are used as intermediate compounds for preparing famotidine or thioclidine, the above problem connected with Compound A (that is, the problem of complicated handling) is avoided. In addition, the compounds of general formula I have the advantage that they can be obtained in high yield and are easy to purify.

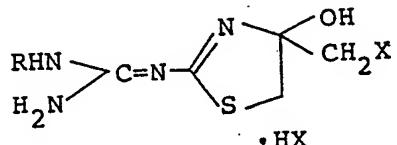
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The compounds of this invention  
can be produced by the following  
cess.

15



20



(I)

25 This process may involve reacting starting material of formula II and a reactive amount of 1,3-dihalogenoacetone of formula III in an

organic solvent under cooling. Any anhydrous organic solvents which do

not take part in the reaction may be used but acetone is preferably used. It is preferred that the reaction 5 temperature be maintained between 0°C and -10°C. In order to obtain the desired compound, the solid material formed in the reaction mixture is collected by solvent e.g. organic solvent such as filtration, and washed with/acetone. The material thus obtained is pure enough to use for the next process as 10 the intermediate material compound.

The following Examples will serve to illustrate the present invention, and the following Reference Examples will further serve to illustrate the preparation of famotidine using the compounds of formula I.

15 In the Examples and Reference Examples, m.p., Anal. and NMR are abbreviations for melting point, elementary analysis values and nuclear magnetic resonance spectrum, respectively.

20 Example 1

N"-[(4-(chloromethyl)-4,5-dihydro-4-hydroxy-2-thiazolyl]-quanidine hydrochloride

25 60.0 kg of dichloroacetone is dissolved in 550 l of acetone. After cooling the solution to -5 ~ -7°C, 55.8 kg of (aminoiminomethyl)thiourea [amidinothiourea] is added to the solution under cooling in 10 kg amounts at hourly intervals.

The mixture is stirred continuously for 5 days below 0°C. The resultant precipitates are collected by filtration, and washed with 50 l of acetone to provide 111.6 kg of the desired compound.

5 This material can be used as the starting material for the next process.

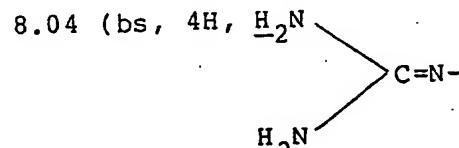
IR (KBr)  $\nu_{\text{max}}$  3200, 2880, 1680, 1595  $\text{cm}^{-1}$

NMR (DMSO-d<sub>6</sub>) δ:

10 3.52 (AB<sub>q</sub>, J=12Hz, 2H, -S-CH<sub>2</sub>-)

3.80 (S, 2H, -CH<sub>2</sub>Cl)

6.96 (bs, 1H, -OH)



15 9.60 (bs, 1H, HCl)

Reference Example 1

N"-[4-[[[(aminoiminomethyl)thio]methyl]-2-thiazolyl]-guanidine dihydrochloride

20 In 500 ml of water are dissolved 111.6 kg of the material obtained in Example 1 and 32.9 kg of thiourea. The solution is stirred for one hour at 50°~55°C to complete the reaction.

25 (N"-[4-[[[(aminoiminomethyl)thio]methyl]-2-thiazolyl]-guanidine dihydrochloride is formed in the reaction mixture, and this reaction mixture

is directly used for the next process without

isolation of the formed compound.

Reference Example 2

N"-[4-[[2-cyanoethyl]thio]methyl]-2-thiazolyl]-

5       guanidine

The reaction mixture obtained in Reference Example 1 is cooled below 10°C, and to the solution are added 45.6 kg of β-chloropropionitrile and 200 l of isopropanol. A solution of 69.1 kg of sodium hydroxide in 280 l of water is added dropwise to the solution under nitrogen stream followed by stirring for 2 hours at 0°C ~ 10°C. The crystals precipitated are collected by filtration, and washed with cold water and dried to provide 91.7 kg of the desired compound.

15       m.p. 125 - 126.5°C.

Reference Example 3

Methyl 3-[[[2-[(diaminomethylene)amino]-4-thiazolyl]-  
methyl]thiolpropionimidate

20       In 60 l of anhydrous dimethylformamide is dissolved 34.3 kg of the material formed in Reference Example 2. After adding 60 l of anhydrous methanol to the solution, 61.9 kg of hydrogen chloride gas is passed through the solution below 5°C. After stirring 25 the reaction mixture for 2 days at 0°C ~ 5°C, the reaction mixture is poured into a mixture of 350 l of water, 250 kg of potassium carbonate, 30 l of ethyl

acetate and ice while stirring below 5°C. The reaction mixture is stirred for 2 hours at 0 ~ 5°C, and the resultant precipitates are collected by filtration.

5 After stirring a mixture of the precipitates and 400 l of water for 0.5 hour at 0°C ~ 5°C, the resultant precipitates are collected by filtration, washed with 40 l of water and 10 l of cooled acetone respectively, and dried at reduced pressure to provide 30.6 kg of the desired product showing a melting point of 125.7°C.

10

## Reference Example 4

3-[[[2-(diaminomethylene)amino]-4-  
thiazolyl]methyl]thio]-N-sulfamoylpropionamidine  
(generic name: famotidine)

15 In 340 l of methanol is dissolved 88.4 kg of sulfamide under heating, and the solution is cooled to 30°C. To the solution, 114.2 kg of the material obtained in Reference Example 3 are added in three portions while stirring at 20 ~ 30°C; the second portion is added 8 hours after the first, and the third portion 24 hours after the first.

20 After stirring the reaction mixture for a further 2 days at 20 ~ 30°C, the crystals formed are collected by filtration, washed with 200 l of cooled methanol, and air-dried at room temperature to provide 87.5 kg of the desired product showing a melting point of 157.6°C. Some of the obtained product is

recrystallized from dimethylformamide-water , and is dissolved in an equivalent molar amount of aqueous acetic acid. To the solution is added an equivalent molar amount of a dilute sodium hydroxide solution in water to separate crystals showing the following physicochemical properties:

I) m.p. 163 ~ 164°C

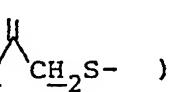
II) Anal. (for  $C_8H_{15}N_7O_2S_3$ )

	C(%)	H(%)	N(%)
Calculated:	28.48	4.48	29.06
Found:	28.37	4.48	28.97

III) NMR (DMSO-d<sub>6</sub>)

2.50 (2H, m, -SCH<sub>2</sub>CH<sub>2</sub>-)

2.65 (2H, m, -SCH<sub>2</sub>CH<sub>2</sub>-)

15  
3.60 (2H, s,  )

6.45 (1H, s,  )

IV) Mass. (FD method) m/e 338

20 Reference Examples 5 and 6 below produce the same products as Reference Examples 1 and 2 above using different reaction conditions:

Reference Example 5

N"-[(4-[(aminoiminomethyl)thio)methyl]-2-thiazolyl]-guanidine dihydrochloride

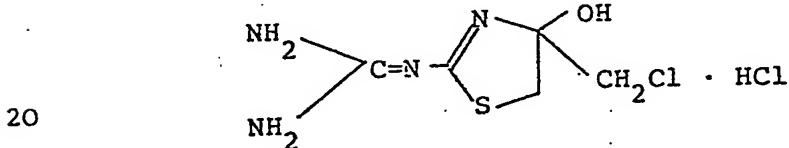
To 111.6 kg of the material obtained in Example 1  
5 are added 500 l of ethyl alcohol and further 31.0 kg of thiourea. The solution is stirred for one hour at 50~55°C, further refluxed under heating for 0.5 hour, and then cooled to 5°C. The crystals formed are collected by filtration, and washed with 60 l of cold ethyl alcohol and air-dried at room temperature to provide 103.5 kg of the desired product showing a melting point of 201~207°C.

Reference Example 6

15 N"-[(4-[(2-cyanoethyl)thio)methyl]-2-thiazolyl]-guanidine

In a mixture of 170 l of iso-propyl alcohol and 500 l of water are dissolved 67.1 kg of the material obtained in Reference Example 5. To the solution are added 23.8 kg of  $\beta$ -chloropropionitrile followed by adding a solution of 35.4 kg of sodium hydroxide in 160 l of water under nitrogen gas atmosphere below 10°C. The reaction mixture is stirred for 1 hour below 10°C, then for 2 hours at 10-15°C, and then 20 cooled to 5°C. The precipitate formed is collected by filtration, and washed with 130 l of water and 30 l of cold iso-propyl alcohol respectively, and then air-dried at room temperature to provide 42.3 kg of 25 the desired product showing a melting point of 125.5°C.

Thus in addition to the formula I compounds and their acid addition salts, the invention provides a method for their preparation. It further provides their use as intermediates for the preparation of corresponding famotidine and thiotaidine compounds (including famotidine and thiotaidine themselves when R is hydrogen); one famotidine compound preparation according to the invention comprises (a) reacting a compound of formula I or an acid addition salt thereof with thiourea (R in formula I being hydrogen for the production of famotidine itself), (b) reacting the reaction (a) product with  $\beta$ -chloropropionitrile in the presence of isopropanol, (c) reacting the reaction (b) product with hydrogen chloride, and (d) reacting the reaction (c) product with sulfamide; a preferred method for the preparation of famotidine comprises (a) reacting the compound of the formula



with thiourea to obtain the compound  
N"-[4-[[(aminoiminomethyl)thiomethyl]-2-thiazolyl]-  
guanidine dihydrochloride;

25 (b) reacting the compound produced in step (a)  
with  $\beta$ -chloropropionitrile in the presence of  
isopropanol to obtain the compound

N"-[(4-[(2-cyanoethyl)thio]methyl]-2-thiazolyl]-  
guanidine;

- (c) reacting the compound produced in step (b)  
with hydrogen chloride to obtain the compound methyl  
5      3-[[2-[(diaminomethylene)amino]-4-thiazolyl]-  
methyl]thio]propionimidate; and  
(d) reacting the compound produced in step (c)  
with sulfamide to obtain famotidine.

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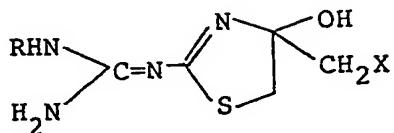
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C L A I M S :

1. 2-Guanidinothiazoline compounds of the general formula

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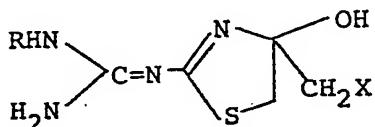
wherein R represents a hydrogen atom or a C<sub>1</sub>-C<sub>5</sub> alkyl group, and X represents a halogen atom, and the acid addition salts thereof.

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2. N"-[4-(chloromethyl)-4,5-dihydro-4-hydroxy-2-thiazoly]-guanidine according to claim 1.

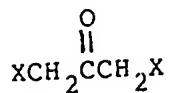
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3. A process for preparing a 2-guanidinothiazoline compound of the formula

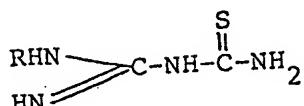


20 as defined in claim 1 or an acid addition salt thereof which comprises reacting 1,3-dihalogenacetone of the general formula

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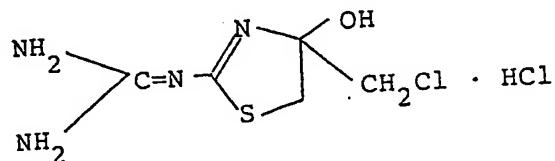
wherein X represents a halogen atom, and  
amidinothiourea of the general formula



wherein R represents a hydrogen atom or a C<sub>1</sub> to C<sub>5</sub> alkyl group.

4. A process for preparing famotidine comprising:

- 10 (a) reacting the compound of the formula



15

with thiourea to obtain the compound  
N"-[4-[(aminoiminomethyl)thio]methyl]-2-thiazoly1-  
guanidine dihydrochloride;

- 20 (b) reacting the compound produced in step (a)  
with β-chloropropionitrile in the presence of  
isopropanol to obtain the compound  
N"-[4-[(2-cyanoethyl)thio]methyl]-2-thiazoly1-  
guanidine;

25

(c) reacting the compound produced in step (b) with hydrogen chloride to obtain the compound methyl 3-[[[2-[(diaminomethylene)amino]-4-thiazolyl]-methyl]thiol]propionimidate; and

5 (d) reacting the compound produced in step (c) with sulfamide to obtain famotidine.

5. A process for preparing a famotidine compound which comprises (a) reacting a compound according to 10 claim 1 with thiourea, (b) reacting the reaction (a) product with  $\beta$ -chloropropionitrile in the presence of isopropanol, (c) reacting the reaction (b) product with hydrogen chloride, and (d) reacting the reaction (c) product with sulfamide.

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EUROPEAN SEARCH REPORT

0128736

Application number

DOCUMENTS CONSIDERED TO BE RELEVANT			EP 84303793.8
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl. 3)
A,D	<p>CHEMICAL ABSTRACTS, vol. 94, no. 17, April 27, 1981, Columbus, Ohio, USA</p> <p>HIRATA, YESUTUMI, "Guanitinothiazolo compounds", page 765, column 1, abstract-no. 139 794w</p> <p>&amp; DE-A1-3 008 056 &amp; JP-A1-56-22 779</p> <p>---</p> <p>CHEMICAL ABSTRACTS, vol. 90, no. 11, March 12, 1979, Columbus, Ohio, USA</p> <p>YELLIN TOBIAS "Guanidine derivatives", page 626, columns 1,2, abstract-no. 87 452d</p> <p>&amp; DE-A1-2 817 078 &amp; JP-A1-53-147 069</p> <p>-----</p>	1,3,4	C 07 D 277/18 C 07 D 277/48// A 61 K 31/425
		1,3,4	
			TECHNICAL FIELDS SEARCHED (Int. Cl. 3)
			C 07 D 277/00
<p>The present search report has been drawn up for all claims</p>			
Place of search	Date of completion of the search	Examiner	
VIENNA	05-09-1984	BRUS	
CATEGORY OF CITED DOCUMENTS		<p>T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons &amp; : member of the same patent family, corresponding document</p>	
<p>X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document</p>			